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Hemoglobin red cell distribution width ratio as a prognostic marker in patients with locally advanced lung adenocarcinoma

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ABSTRACT

Aims: Hemoglobin/red cell distribution width ratio (HRR) has been defined as an effective prognostic factor in various malignancies. The aim of this study is to investigate the prognostic role of HRR in locally advanced lung adenocarcinoma.

Methods: 626 patients diagnosed with locally advanced lung adenocarcinoma were screened. The best cut-off point of HRR for overall survival (OS) and progression free survival (PFS) was determined by ROC analysis. A HRR cut-off value was determined, patients were classified as having lower or higher HRR. Both groups' clinical, demographic, laboratory values were compared. To identify independent predictors of prognosis, multivariate cox regression analysis was used.

Results: A total of119 patients were included. The best cut-off point of HRR in determining OS was 0.963%.HRR below the cut-off value increased mortality by 2.2fold.The group with HRR<0.963% had higher mean age and RDW and lower mean albumin. At the same time, the 5-year OS value of the group with HRR ≥0.9632 was 52.6% and the median OS of this group was 62.7months,while the 5year OS vale of the group with HRR <0.9632 was 24.7% and the median OS was 32.4 months. In multivariate cox-regression analysis, HRR was not independent predictor of mortality risk.

Conclusion: HRR is a potential biomarker for prognosis in patients with locally advanced lung adenocarcinoma.

Keywords: Hemoglobin red cell distribution width ratio, mortality, OS

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INTRODUCTION

RDW is thought to be a potential marker for oxidative stress, endothelial damage, and the inflammatory process that leads to neoplasm development.[1] A high RDW value is associated with systemic inflammation and therefore with aggressive tumor behavior.[2] In studies, high RDW has been associated with increased mortality in lung cancer.[3] At the same time, detection of anemia before treatment is associated with poor outcomes in oncology patients .[4]

Although low Hb and high RDW values are associated with poor progression free survival (PFS) and overall survival (OS) in a variety of cancers, it is debatable whether these values alone can predict tumor behavior because they are influenced by the inflammatory process. As a result, the Hb/ RDW (HRR) can help to reduce potential bias.[5-8]

HRR was first proposed as a prognostic factor biomarker to determine overall survivor in esophageal squamous cell carcinoma patients, followed by a similar study in lung small cell carcinoma patients, and in 2021, the usefulness of preoperative HRR values on resected lung adenocarcinoma as a biomarker to determine patient prognosis was emphasized.[9-11]

The HRR value is a potential biomarker as it is simple to calculate and the parameters that comprise this ratio are inexpensive. In our study, we examined the prognostic sensitivity of HRR in patients with locally advanced lung adenocarcinoma by excluding factors that could cause an inflammatory response and thus affect the HRR value.

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METHODS

The study was carried out with the permission of Ankara Atatürk Sanatorium Training and Research Hospital Ethics Committee (Date: 26.04.2023 Decision No: 2628). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was planned retrospectively. 4,785 lung adenocarcinoma patients who applied to our hospital between January 2010 and January 2020 were screened. 626 patients had locally advanced lung adenocarcinoma. Considering the inclusion criteria, 119 patients were included in the study.

These criteria were that the patient should be older than 18 years of age, all clinical, laboratory, treatment, pathology and imaging data should be available, the patient should have locally advanced lung adenocarcinoma according to the 8th TNM staging, and there should be no comorbidities such as diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), secondary cancer, concomitant infection, inflammatory disease or lymphoproliferative disease that may affect the HRR value.[8,9] Gender, age, smoking history, malignancy stage, treatments received, total follow-up time, PFS, OS values, laboratory values (albumin g/dl, hemoglobin g/dl, neutrophil mcl, lymphocyte mcl, platelet u/ml, RDW fL) were recorded. Hemoglobin/RDW% (HRR), neutrophil/lymphocyte % (NLR), platelet/lymphocyte % (PLR) values were calculated.

The best cut-off point of HRR value in determining OS and PFS was determined according to ROC analysis. Patients were divided into two groups according to the cut-off value. Clinical characteristics, OS and PFS times were compared.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY, USA). The optimal threshold for HRR in order to predict prognosis (i.e., progression free and overall survival) was evaluated ROC analysis. Sensitivity, specificity, positive and negative predicted values, and accuracy levels for HRR were also calculated. While the mean differences between groups were compared Student's t test, otherwise the Mann Whitney U test was applied for comparisons of not normally distributed variable. Cumulative survival rates for 1, 3, and 5 years, mean expected duration of life and 95% confidence intervals were computed by Kaplan-Meier survival analysis. Whether the potential factors were statistically significant effect on prognosis or not was investigated univariate Cox's proportional hazard regression models. Multiple Cox's proportional hazard regression model was obtained to determine the best independent predictors which mostly affected on prognosis after adjustment for clinically important factors. A p value less than 0.05 was considered statistically significant.

RESULTS

Among 626 locally advanced lung adenocarcinoma patients, 356 patients were excluded from the study due to comorbidities that would affect the HRR value. 119 patients were included in the study. 87.4 % of the cases were male. The mean age was 60.4±9.5 years. The most common stage in the study was Stage IIIA with 40.4 % (**Table 1**). Mean RDW value was 15.1 fL (±1.67), albumin value was 3.8 g/dl (3.5-4.2), NLR value was 2.71 (1.96-3.59)%, PLR value was 115.6 (82.6-180.8) %, and HRR value was 0.94 (±0.16) % (**Table 1**). The mean PFS was 36.5 months, and the mean OS was 44.3 months. The best cut-off point of HRR in determining OS and PFS was obtained by ROC analysis (**Table 2**). The best cut off point of HRR for OS was 0.963% (p=0.042) (**Figure**). HRR below the cut off value was associated with a 2.2-fold increase in mortality (**Table 3**). Demographic and clinical characteristic of the patients were compared according to the HRR cut-off value (**Table 4**). The group with HRR<0.963 had higher mean age and RDW fL (p=0.020 and p<0.001) and lower mean albumin g/dl (p<0.001) (**Table 4**). At the same time, the 5-year OS of the group with HRR≥0.9632 was 52.6% and the mean OS of this group was 62.7 months (95% CI: 48.0-77.4), while the 5-year OS of the group with HRR<0.9632 was 24.7% and the mean OS was 32.4 months (95% CI: 23.6-41.1).

In multivariate cox-regression analysis, stage, lack of treatment, and advanced age were independent factors in determining OS, whereas HRR was not an independent factor in determining OS and PFS. (**Table 3**).

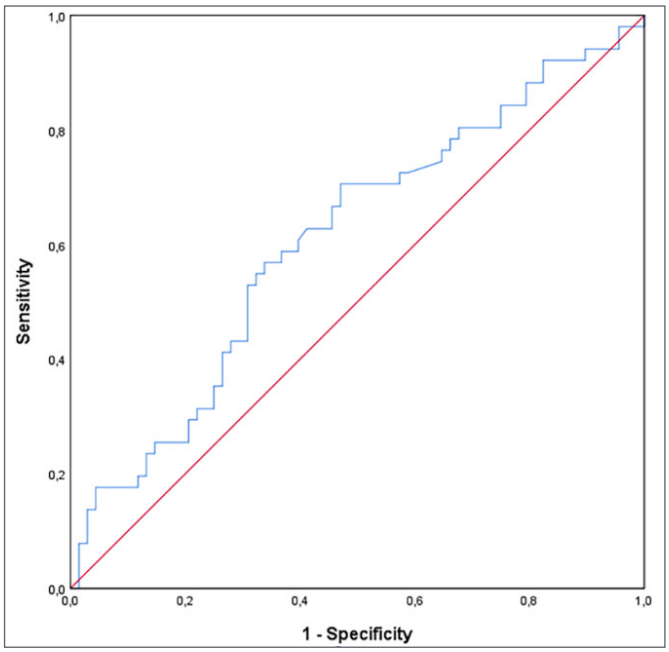

Figure. ROC curve of HRR measurements

Table 1. Demographic and clinical characteristics of the patients

	n=119
Age (year)	60.4±9.5 (35-86)
Sex	
Female	15 (12.6%)
Male	104 (87.4%)
Stage	
IIA	4 (3.4%)
IIB	24 (20.2%)
IIIA	48 (40.4%)
IIIB	30 (25.1%)
IIIC	13 (10.9%)
Treatment	
None	23 (19.3%)
Operated	12 (10.1%)
Chemoradiotherapy	18 (15.1%)
Radiotherapy	2 (1.7%)
Chemotherapy	27 (22.7%)
Operated and Chemoradiotherapy	34 (28.6%)
Operated and Chemoradiotherapy	3 (2.5%)
Smoking History	
None	18 (15.1%)
Quit	64 (53.8%)
Smoking	37 (31.1%)
RDW*	15.1±1.67
Albumin	3.8 (3.5-4.2)
NLR*	2.71 (1.96-3.59)
PLR*	110.6 (81.2-167.2)
HRR*	0.94±0.16
Progression	44 (37.0%)
Total Follow-up Duration	12.3 (4.8-31.7)
Recovery	
Alive	68 (57.1%)
Deceased	42.9%)

*RDW: Red cell distribution width NLR: Neutrophil-lymphocyte ratio PLR: Platelet-lymphocyte ratio HRR: Hemoglobin Red Cell Distribution Width Ratio

Table 2. ROC analysis of HRR as best cutoff to determine OS and PFS

	PFS	OS
AUC	0.525	0.609
95% CI	0.414-0.636	0.506-0.713
p-volume	0.652	0.042
Best cut off	-	<0.9632
Sensitivity	-	70.6%
Specificity	-	52.9%
PPV	-	52.9%
NPV	-	70.6%
Accuracy	-	60.5%

PFS: Progression free survival, OS: Overall survival, AUC: Area under the curve, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

Table 4. Comparison of demographic and clinical characteristics of HRR groups

	HRR ≥0.9632 (n=51)	HRR < 0.9632 (n=68)	p value
Age (year)	58.1±7.7	62.1±10.4	0.020†
Sex			0.028‡
Female	2 (3.9%)	13 (19.1%)	
Male	49 (96.1%)	55 (80.9%)	
Stage			0.673¶
IIA	3 (5.9%)	1 (1.5%)	
IIB	9 (17.7%)	15 (22.1%)	
IIIA	22 (43.1%)	26 (38.2%)	
IIIB	12 (23.5%)	18 (26.5%)	
IIIC	5 (9.8%)	8 (11.7%)	
Treatment			
None	7 (13.7%)	16 (23.5%)	0.269‡
Surgery	26 (51.0%)	23 33.8%)	0.090‡
Chemoradiotherapy	11 (21.6%)	10 (14.7%)	0.466‡
Radiotherapy	0 (0.0%)	2 (2.9%)	0.506¥
Chemotherapy	25 (49.0%)	36 (52.9%)	0.812‡
Smoking History			0.373¶
None	5 (9.8%)	13 (19.1%)	
Quit	29 (56.9%)	35 (51.5%)	
Smoking	17 (33.3%)	20 (29.4%)	
RDW	14.2±1.03	15.8±1.73	<0.001†
Albumin	4.0 (3.7-4.4)	3.6 (3.4-4.0)	<0.001§
NLR	2.65 (1.78-3.53)	2.79 (2.06-3.65)	0.342§
PLR	105.6 (82.6-152.4)	113.1 (76.4-179.0)	0.599§

† Student's t test, ‡ Continuity corrected $\chi 2$ test, ¶ Pearson's $\chi 2$ test, ¥ Fisher's exact test, § Mann Whitney U test.

Table 3. Results of univariate and multivariate Cox's proportional hazards regression analysis on overall survival

	Univariate			Multivariate		
	HR (95% CI)	Wald	p-value	HR (95% CI)	Wald	p-value
Age	1.045 (1.016-1.075)	9.187	0.002	1.036 (1.001-1.072)	4.156	0.041
Male	0.897 (0.381-2.111)	0.062	0.803	-	-	-
Stage	1.301 (0.983-1.722)	3.389	0.066	1.538 (1.124-2.105)	7.239	0.007
No treatment	3.140 (1.708-5.771)	13.566	<0.001	2.509 (1.246-5.054)	6.632	0.010
Surgery	0.224 (0.111-0.452)	17.412	<0.001	-	-	-
Chemotherapy	0.586 (0.336-1.023)	3.539	0.060	-	-	-
Radiotherapy	5.179 (0.682-39.354)	2.526	0.112	-	-	-
Chemoradiotherapy	0.836 (0.404-1.729)	0.233	0.629	-	-	-
Smoking History	1.357 (0.538-3.421)	0.417	0.518	-	-	-
RDW	1.152 (0.983-1.349)	3.053	0.081	0.963 (0.793-1.171)	0.141	0.707
Albumin	0.665 (0.393-1.125)	2.309	0.129	-	-	-
NLR	1.006 (0.846-1.195)	0.004	0.948	-	-	-
PLR	1.002 (0.999-1.006)	1.613	0.204	-	-	-
HRR	0.189 (0.032-1.110)	3.402	0.065	-	-	-
HRR <0.9632	2.182 (1.188-4.010)	6.322	0.012	1.994 (0.975-4.077)	3.576	0.059

RDW: Red cell distribution width NLR: Neutrophil-lymphocyte ratio PLR: Platelet-lymphocyte ratio HRR: Hemoglobin Red Cell Distribution Width RatioHR: Hazard ratio, CI: Confidence interval.

DISCUSSION

It was determined in the study that HRR <0.963 increased the mortality rate by 2.2 times in patients with locally advanced lung adenocarcinoma. Patients with lower HRR values had a shorter 5-year OS, lower albumin, and higher RDW values.

Lung adenocarcinoma constitutes 60% of non-small cell lung cancers and new prognostic markers are needed in diagnosis and follow-up due to high mutation rates.[14] RDW has recently been used in cancer patients as a prognostic marker in addition to determining the type of anemia. A 2017 meta-analysis of the prognostic impact of RDW on cancers, which included 16 articles and 4,267 patients, discovered that high RDW was associated with poor OS and PFS.[15] There are conflicting results in lung cancer. Koma et al.[16] in a study of 332 lung cancers showed that high RDW reflected inflammation and malnutrition and was associated with poor OS. In another study conducted in 2016, no statistically significant results were found for RDW as a prognostic marker in lung cancer.

The prognostic effect of HRR on patients with squamous cell carcinoma of the esophagus was first investigated by Sun et al.[9] In the study of 362 patients, the group with HRR <0.989 had lower 5-year OS (33.7% vs. 55.5%) and median OS (89.8 months vs. 81.7 months) than the group with HRR ≥ 0.989. Although HRR below the cut off value increased the mortality rate 1.416 times, it was found that NLR, PLR and RDW values were higher in the group with HRR<0.989.[9] In our study, there was no significant difference in NLR and PLR values between the low HRR (<0.963) and high HRR (<0.963) groups, while albumin value, which indicates increased inflammation, tumor burden, and malnutrition, was lower and RDW value was higher. The finding of low albumin and high RDW in the group with low HRR supports the association of HRR with mortality. There have been few studies on the value of HRR in predicting prognosis in lung cancer patients. Low HRR was discovered to be an independent factor in determining OS and PFS in a study of 153 patients with advanced non-small extracellular lung carcinoma.[18] In a study conducted by Ergur et al.[19] on 840 small cell lung cancers, it was found that low HRR increased the risk of death by 1.6 times. Petrella et al.[11] reported that preoperative HRR value was an effective prognostic factor for disease-free survival with pathologic lymph node involvement in resected lung adenocarcinoma patients.[13] While the cut-off value of HRR was 0.88 in the study of Bozkaya et al.[18] and 1.01 in the study of Petrella et al.[11] and 0.580 in the study of Ergur et al.[19] in our study, the HRR value was 0.963.

Finally, in a meta-analysis of 11 studies involving 2,985 patients, it was found that a low HRR value increased the risk of death and recurrence by twofold in cancer patients in 2022.[20] Since lung cancer has many subtypes and high mutation diversity, this study focused on locally advanced lung adenocarcinoma. By excluding all comorbidities and secondary malignancies that would affect the Hb and RDW parameters that comprise the HRR value, the effect of HRR on a specific malignancy group, such as locally advanced lung adenocarcinoma, was more clearly seen. The limitations of our study are the retrospective nature of the study and the lack of a standard cut-off value for HRR.

CONCLUSION

Low HRR value is associated with lower OS in patients with Locally Advanced Lung Adenocarcinoma. HRR is a potential biomarker. To show that it is an independent factor, many more prospective studies are needed in which all factors are taken into account.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Atatürk Sanatorium Training and Research Hospital Ethics Committee (Date: 26.04.2023, Decision No: 2628).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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